Docket No. MCP 264

#13

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Codispoti, Joseph R.

Serial No. : 09/709,069 Art Unit: 1614

Filed : 9 November 2000 Examiner: Jagoe, D.

For : METHOD FOR TREATING MIGRAINE SYMPTOMS WITH IBUPROFEN

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on

23 May 2002
(Date of Deposit)

Michele G. Mangini
(Name of applicant, assignee, or Registered Representative

Michele Mangini
(Signature)

23 May 2002
(Date of Signature)

Assistant Commissioner For Patents
Washington, D.C. 20231

SUPPLEMENTAL DECLARATION UNDER 37 CFR 1.131

Dear Sir:

1. This Supplemental Declaration is submitted to supplement the Declaration Under 37 CFR 1.131 mailed on 25 August 2000 in response to the 30 March 2000 Office Action in the parent application, United States Serial No. 09/449,124 (herein "Declaration"). During the prosecution of the above-referenced application, I became aware of the fact that the Declaration contained an inadvertent typographical error in the page number listed for the Furey Abstract. This inadvertent error is corrected in Paragraph 2 herein.

2. This Supplemental Declaration is submitted to establish completion and reduction to practice of the invention in the above-identified application in the United States at a date prior to 24 August 1999. It is my information and belief that the Information Center of McNeil Consumer & Specialty Pharmaceuticals Division of McNeil-PPC, Inc., the assignee of record to the entire right, title, and interest in the above-identified application (hereinafter "Assignee"), received a copy of the abstract entitled "Efficacy and Safety of Ibuprofen (I) Liquigels in Migraine Headache: A Randomized, Double-Blind Placebo-Controlled Study" by Furey, et al., as published in Volume 39(9) of the Journal of Clinical Pharmacology on page 978 (Sept. 1999) (hereinafter "Furey Abstract"), on or about 24 August 1999. It is further my information and belief that this volume of the Journal of Clinical Pharmacology was mailed to its subscribers on or about 20 August 1999. A copy of the Furey Abstract is attached hereto as Exhibit A. The Furey Abstract was cited in the Office Action mailed on 27 February 2002 in the above-referenced application.

3. I, Joseph R. Codispoti, MD, am the sole inventor on the invention described and claimed in the above-identified application.

4. As of approximately August 2001 until the present, I am employed by Sanofi-Synthelabo Research and Development located at 9 Great Valley Parkway, Malvern, PA 19355. Previous to that date, and at and before the completion of the invention, I was in the employ of the Assignee.

5. I understand that the claims of the present invention have been rejected in view of the Furey Abstract.

6. Appended hereto as Exhibit B is a true copy of the Clinical Study Report entitled "A Single Dose, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Ibuprofen 200 mg and 400 mg for the Treatment of Migraine Headache Pain (hereinafter "Report"), which was performed at my request and which memorializes the conception and reduction to practice of the claimed invention.

7. On page 12 of the Report, it can be seen that the invention of this application, i.e. a method for mitigation or treating photophobia and phonophobia associated with migraines by providing an effective amount of ibuprofen as the sole anti-migraine agent, was made prior to August, 1999, which is earlier than the 35 USC §102(f) date of the Furey Abstract.

8. All dates that have been redacted in the Exhibit are before August, 1999.

8. I, Joseph R. Codispoti, further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further declare that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 35 USC §1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or patent issuing thereon.

By: _____ MD
Joseph R. Codispoti, MD

Country of Citizenship: USA

Address: 1300 Worthington Rd, Phila, PA

Date: 5/23/2002

Att.
Appendix A: Furey Abstract
Appendix B: Clinical Study Report

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Official Publication of the American College of Clinical Pharmacology

COMPLETE CONTENTS INSIDE

Abstracts of the 28th Annual Meeting of the American College of Clinical Pharmacology
September 16-18, 1999
Rockville, Maryland

JOB
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Exhibit A

1999/261
I6286

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EFFICACY AND SAFETY OF IBUPROFEN (I) LIQUIGELS IN MIGRAINE HEADACHE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY. S.A. Foyer[2], D. Kellstein[1]°, R. Gomba[1]°, B. An[1]°, P. Consilio[1]°, J. Saper[2]°. [1]Medical Department, Whitehall-Robins Healthcare, Madison, NJ and [2]Michigan Head•Pain & Neurological Institute, Ann Arbor, MI.

We compared I 400mg and I 600mg administered as liquigels to placebo (PBO) among subjects with moderate or severe migraine headache at baseline. At 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 24h after dosing subjects rated pain intensity on a four-point and rated pain relief on a five-point categorical scale. Subjects also rated the associated migraine symptoms of nausea, photophobia, and phonophobia, and assessed their limitation of activity (LOA) using a quality of life index ranging from 0 (none) to 3 (severe). The primary endpoint was the cumulative % of responders by 2h: a responder was a subject whose pain intensity was reduced from severe or moderate at baseline to mild or none postdosing. We noted the following results:

Endpoint	PBO (n=169)	I 400mg (n=209)	I 600mg (n=219)
Cumulative responders 2h (%)	41	57*	59*
SPRID (0-6h)	7.0	9.9*	10.1*
Median 1st perceptible relief (min)	66	47*	42*
LOA improvement (6h)	0.5	1.0*	0.9*
Nausea improvement (6h)	0.2	0.5*	0.5*

(* p<0.05 vs. PBO); I 400mg and 600mg were both significantly superior to PBO in the cumulative % of subjects with no nausea, photophobia, and phonophobia over 6h. I 600mg tended to demonstrate a small numerical advantage over 400mg. I 400mg and 600mg were well-tolerated, with adverse experience incidences comparable to PBO. Based on these data, we conclude that I 400-600mg effectively relieves migraine pain, reduces ancillary migraine symptoms, and improves migraineurs' quality of life; the shallow dose-response seen here makes I 400mg the preferred migraine dose.

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PHARMACOKINETICS OF EMD 132 338 AFTER ESCALATING SINGLE ORAL DOSES OF GANTOFIBAN, A NEW GLYCOPROTEIN IIB/IIIA RECEPTOR ANTAGONIST. Bernd Meibohm, Roland Neugebauer°, Karl-Ulrich Bühring°, Michael Schulte°, and Andreas Kovar°. College of Pharmacy, University of South Carolina, Columbia, SC and Clinical Pharmacology, Merck KGaA, Darmstadt, Germany.

Gantofiban is an orally available double prodrug. Bioactivation results in the active metabolite EMD 132 338, a potent, reversible, non-peptide antagonist of the glycoprotein IIb/IIIa receptor (GPR) for the inhibition of platelet aggregation associated with thromboembolic events. In a phase I clinical study, the pharmacokinetics of EMD 132 338 were evaluated in sequential groups of healthy male subjects after single oral doses of 2.5 (n=9), 5 (n=9), 7.5 (n=7), and 10 (n=6) mg gantofiban, respectively. Total (GPR bound & unbound) plasma concentrations of EMD 132 338 were monitored for 48 hours post-dose using a validated HPLC assay, and were subjected to noncompartmental pharmacokinetic analysis. After oral administration, gantofiban is rapidly absorbed and converted into its active metabolite EMD 132 338. Maximum plasma concentrations C_{max} were reached after a t_{max} of 1.53 ± 0.92 h (mean ± SD). C_{max} followed dose-proportionality, ranging between 3.5 - 20.7 ng/mL with a relatively small interindividual variability at all dose levels (CV ~25%). The area under the curve AUC_∞ also increased dose-dependently but less than necessary for formal dose-proportionality, most likely due to an increased elimination of EMD 132 338 at concentrations beyond saturation of the binding to the GPR. EMD 132 338 further exhibited a dose-independent, long terminal half life of 21.2 ± 6.0 h. Thus, EMD 132 338 is characterized by predictable and reproducible pharmacokinetics with a long terminal half life favorable for long-term oral therapy.

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EFFECT OF NEVIRAPINE ON HUMAN BLOOD GLUTATHIONE LEVELS AND SUBCHRONIC TOXICITY AFTER DERMAL ADMINISTRATION TO RATS. Chukwuemeka S. Okereke. Univ. of Rhode Island College of Pharmacy, Roger Williams Med. Cent. Providence, RI.

Nevirapine (NVP) is a potent non-nucleoside reverse transcriptase inhibitor that has been shown to inactivate the human immuno-deficiency virus upon administration. Currently, attempts at reducing incidences of vertical transmission of the virus (mother to child) have focused on the use of pharmacological agents in "birth canal cleansing" during child labor and delivery. Following subchronic administration of NVP to female rats twice daily for 4-weeks, body weight, clinical chemistry and hematological parameters were not affected. However, invivo blood glutathione (GSH) was reduced. Similarly, invitro blood GSH time course in humans and rats were reduced initially up until 45 minutes and gradually returned to control levels thereafter. The rebound in GSH levels is probably due to a compensatory mechanism due to GSH-reductase enzyme. Based on these studies, NVP does not seem to produce any appreciable dermal effects in rats.

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GABAPENTIN SINGLE-DOSE PHARMACOKINETICS IN HEALTHY INFANTS AND CHILDREN Grace M. Haig°, Howard N. Bockbrader°, David L. Wesche°, Samuel W. Boellner°, Richard Brown°, Nancy Janiczek-Dolphin°, and Edward L. Posvar, Parke-Davis Pharmaceutical Research; Ann Arbor, MI.

Gabapentin (Neurontin) is a gamma-aminobutyric acid analogue indicated in adults for adjunctive treatment of partial seizures with or without secondary generalization. Two studies were conducted to determine the single-dose pharmacokinetics of gabapentin in healthy subjects age 1 month to 12 years and to guide dose selection in safety and efficacy trials in pediatric patients for the above indication. Forty-eight subjects were given a single dose of gabapentin 10 mg/kg administered orally while fasting. Enrollment was homogeneously distributed throughout the age range. Plasma samples were drawn pre-dose, then serially for 24 hours. A single dose of gabapentin was well tolerated by healthy pediatric subjects. Plots of age vs. AUC(0-∞) suggested differences in younger (1 month to 4 years) vs. older (5 to 12 years) subjects. Mean AUC(0-∞) was 25.7 µg·hr/mL in younger subjects and 36.0 µg·hr/mL in older subjects (p<0.001). Clearance (normalized to weight) was 7.35 mL/min/kg for younger subjects and 4.41 mL/min/kg for older subjects (p<0.001). Mean peak plasma concentrations (Cmax) were 3.74 and 4.52 mcg/mL, respectively (p<0.05). Differences in the calculated bioavailability could not sufficiently explain the disparity in AUC. Patients between 1 month and 4 years would require an approximate 30% larger daily dose to achieve similar drug exposures to those patients between 5 and 12 years of age.

Appendix II.

MCNEIL CONSUMER HEALTHCARE

CLINICAL STUDY REPORT

PROTOCOL [redacted]

PHASE III

A Single-Dose, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Ibuprofen 200 mg and 400 mg for the Treatment of Migraine Headache Pain.

START DATE: [redacted]

END DATE: [redacted]

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Report No.

[redacted]
Report Date

Daniel G. Gawarecki, MS
Biostatistician,
Statistical Services

[redacted]
Date

Brenda Zimmerman, MS
Assistant Director,
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Date

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Date

Vanessa Burczynski, BS
Medical Program
Administrator,
Clinical Development

[redacted]
Date

Joseph R. Codispoti, MD
Director,
Clinical Development

[redacted]
Date

Exhibit B

Clinical Study Report
Ibuprofen Tablet 200mg
McNeil Consumer Healthcare

1. SYNOPSIS

Name of Sponsor/Company McNeil Consumer Healthcare ***Name of Finished Product:*** Motrin Migraine (Ibuprofen Tablet 200 mg) ***Name of Active Ingredient:*** Ibuprofen	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of study: A Single-Dose, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Ibuprofen 200 mg and 400 mg for the Treatment of Migraine Headache Pain.

Investigators: The 18 investigators are listed in Section 4, Investigators and Study Administrative Structure

Study Centers: The 18 investigative sites are listed in Section 4, Investigators and Study Administrative Structure

Study period:

Phase of development: III

Objectives: The purpose of this study was to evaluate the efficacy and safety of ibuprofen 200 mg and ibuprofen 400 mg for the treatment of pain associated with migraine headache.

Methodology: This was a multicenter, single-dose, randomized, double-blind, parallel, placebo-controlled study of approximately 600 subjects, 18 years of age and older, experiencing at least moderate pain associated with migraine headache. Following a screening visit, eligible subjects were randomly assigned to either ibuprofen 200 mg, ibuprofen 400 mg or placebo. Subjects left the investigative center with one dose of blinded study drug, a timing device, and a subject diary. After the occurrence of a migraine headache of at least moderate intensity, subjects dosed with study medication and recorded in the diary the date and time of study medication administration. Efficacy and safety were assessed at specified intervals for six hours following the use of study medication. Subjects returned to the site for a follow-up visit within 72 hours after dosing with study medication.

Number of subjects:
This study was designed for the completion of at least 600 subjects. Data were available for 649 subjects, all of whom were included in an intent-to-treat efficacy analysis. All subjects who dosed with study medication and who had efficacy data were included in the intent-to-treat analysis. Data were available for 641 subjects in the per-protocol analysis. The table below summarizes the distribution of these subjects by treatment group:

	Ibu 200 mg	Ibu 400 mg	Placebo	Total
Enrolled	240	239	234	713
Intent-to-Treat	216	219	214	649
Per-Protocol	214	214	213	641

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Name of Sponsor/Company McNeil Consumer Healthcare *Name of Finished Product:* Motrin Migraine (Ibuprofen Tablet 200 mg) *Name of Active Ingredient:* Ibuprofen	*Individual Study Table Referring to Part of the Dossier* *Volume:* *Page:*	(For National Authority Use Only)

The table below summarizes the demographic characteristics for all subjects enrolled:

Characteristic	Ibu 200 mg (N = 240)	Ibu 400 mg (N = 239)	Placebo (N =234)	Total (N = 713)
Sex (n,%)				
Male	42 (17.5)	35 (14.6)	34 (14.5)	111 (15.6)
Female	198 (82.5)	204 (85.4)	200 (85.5)	602 (84.4)
Mean age (yrs)	38.9	38.5	38.2	38.6
Race (n,%)				
Caucasian	214 (89.2)	200 (83.7)	208 (88.0)	620 (87.0)
African-American	15 (6.2)	18 (7.5)	12 (5.2)	45 (6.3)
Other	11 (4.6)	21(8.8)	16 (6.8)	48 (6.7)

Diagnosis and main criteria for inclusion: Migraine headache. Subjects were required to have history of one migraine headache every two months to six migraine headaches per month that were not debilitating or incapacitating.

Test product, dose and mode of administration, batch number: Study drug treatment was Motrin IB, 200 mg and 400 mg, oral tablet, control number C-778-1B.

Duration of treatment: Subjects were treated with a single dose of study drug when they experienced a migraine. Subjects were evaluated for six hours after starting treatment. After dosing with study medication, subjects returned to the investigative site for a follow-up visit.

Reference therapy, dose and mode of administration, batch number: Reference therapy consisted of an oral placebo tablet, control number C-220-6A.

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was the percentage of subjects who experienced a reduction in baseline pain intensity from severe (3) or moderate (2) to mild (1) or none (0) at the two hour postmedication assessment time (defined as "responders"). An additional primary efficacy endpoint was the pain intensity difference from baseline at two hours. Secondary measures of efficacy included: percentage of subjects pain free at two hours; percentage of subjects with associated migraine symptoms reduced to zero at two and six hours; time to rescue and rescue rate; pain intensity differences from baseline and pain relief from 0.5 to 6 hours; SPID, TOTPAR, severity differences from baseline for the associated migraine symptoms from 0.5 to 6 hours; emergence of associated symptoms; subject rating of overall impression of medication; and time to and intensity of recurrent headaches.

Safety: Safety assessments consisted of a routine physical examination at baseline and monitoring of adverse events.

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Statistical Methods: There were three pairwise comparisons of interest for analysis: ibuprofen 200 mg vs. placebo, ibuprofen 400 mg vs. placebo, and ibuprofen 200 mg vs. ibuprofen 400 mg. Each of the statistical tests described below were performed for each treatment pair at the 0.05, two-tail alpha level. The intent-to-treat analysis was the primary analysis.

Primary Measures:
A Cochran-Mantel-Haenszel test of general association stratified by baseline level of pain intensity was used to make pairwise treatment comparisons of response rates. A three-way ANOVA (Treatment, Baseline Pain, Investigator) was used in the analysis of pain intensity difference (PID) from baseline at two hours; pairwise treatment comparisons were made using Fisher's protected LSD technique.

Additional pain measures:
The percent of subjects who were pain free was analyzed with a Cochran-Mantel-Haenszel test of general association, stratified by initial level of pain intensity. PIDs at times other than two hours and SPID were analyzed similarly to the analysis of PID at two hours. A two-way ANOVA (Treatment, Investigator) was used for the analysis of pain relief (PR) at each time point; TOTPAR was analyzed similarly.

Associated symptoms:
For subjects reporting each symptom at baseline, differences from baseline in severity of nausea, photophobia, phonophobia, and functional disability at each measurement interval during the six-hour follow-up period were analyzed using analysis techniques identical to those outlined for PID above with the exception that the baseline severity of each individual symptom was included in the ANOVA model in place of baseline headache pain intensity. The rates of emergence of each associated symptom after baseline were analyzed using Fish r's exact tests. Pairwise treatment comparisons of the percentage of subjects with the severity of nausea, photophobia, phonophobia, and functional disability reduced to "none" at two and six hours were analyzed with Cochran-Mantel-Haenszel tests of general association stratified by baseline level of each symptom. The incidence of vomiting combined across all measurement intervals was compared using Fisher's Exact tests.

Other measures:
Pairwise treatment comparisons for the overall impression of the study medication were made using the extended Cochran-Mantel-Haenszel test with mean modified ridit scores, stratified by initial level of pain intensity. Pairwise treatment comparisons of time to recurrence of migraine headache were performed using the Wilcoxon test available in the SAS© LIFETEST procedure. Only subjects who were "responders" at two hours and had a recurrence of moderate or severe migraine were included in the analysis. Pairwise treatment comparisons of severity of the pain associated with the recurrent migraine headache were analyzed using a Cochran-Mantel-Haenszel test of general association, stratified by initial level of pain intensity. Only subjects with a recurrent migraine headache were included in this analysis.
Pairwise differences in the survival distributions between treatments for the time to rescue were conducted using the Wilcoxon test available in the SAS© LIFETEST procedure. Rescue rates at six hours were analyzed using a Cochran-Mantel-Haenszel test, stratified by initial level of pain intensity.

Subgroup analyses:
The two primary measures were analyzed by baseline pain, gender, and race. In addition, the percentage of responders at two hours was analyzed by menstrual status (yes/no).

Safety Measures:
The frequency of adverse events and frequency of withdrawal from the study were compared between treatment groups with chi-square tests.

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Name of Active Ingredient: ibuprofen	*Page:*	

Efficacy Results: Key demographic and baseline characteristics of the intent-to-treat population are given below:

Characteristic	Ibu 200 mg (N = 216)	Ibu 400 mg (N = 219)	Placebo (N = 214)	Total (N = 649)
Sex (n,%)				
Male	36 (16.7)	33 (15.1)	28 (13.6)	98 (15.1)
Female	180 (83.3)	186 (84.9)	185 (86.4)	551 (84.9)
Mean Age (yrs)	38.8	38.5	38.5	38.6
Race (n,%)				
White	191 (88.4)	185 (84.5)	191 (89.2)	567 (87.4)
African-American	14 (6.5)	15 (6.8)	11 (5.1)	40 (6.2)
Other	11 (5.1)	19 (8.7)	12 (5.6)	42 (6.5)
Baseline Pain (n,%)				
Moderate	144 (66.7)	158 (72.1)	152 (71.0)	454 (70.0)
Severe	72 (33.3)	61 (27.9)	62 (29.0)	195 (30.0)

The key efficacy results from this study are summarized in the table below:

				Significance[a]		
Endpoint	Ibu 200	Ibu 400	Placebo	Ibu 200 vs Placebo	Ibu 400 vs Placebo	Ibu 200 vs Ibu 400
Pain to mild or none at 2 hours[b] (%)	30.81	41.10	26.64	S	S	NS
Baseline Pain = Moderate	49.31	45.57	28.95	S	S	NS
Baseline Pain = Severe	20.89	29.51	20.97	NS	NS	NS
PID at 2 hours[b] (mean)	0.67	0.66	0.39	S	S	NS
Baseline Pain = Moderate	0.58	0.51	0.14	S	S	NS
Baseline Pain = Severe	0.91	1.02	0.85	NS	NS	NS
Pain to none at 2 hours (%)	13.43	15.98	8.64	S	S	NS
SPID (mean)	4.17	4.01	2.05	S	S	NS
TOTPAR (mean)	9.63	9.52	5.55	S	S	NS
Overall Impression of Medication (mean)	1.14	1.14	0.56	S	S	NS
Recurrence within 24 hours (%)	31.4	31.1	33.3	NS	NS	NS

a: S: $p \leq 0.05$; NS: $p > 0.05$.
b: Primary endpoint

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In addition to these results, there was a significantly greater reduction from baseline in mean severity of migraine-associated symptoms of photophobia and functional disability in both ibuprofen groups compared t placebo at all time points in the interval from two to six hours after dosing. For phonophobia, mean severity differences were significant only for the 400 mg ibuprofen dose relative to placebo from one to six hours and for nausea, there were no differences between treatments at any time interval.

Safety Results: Ibuprofen was well tolerated and no safety issues were identified in this migraine headache population. Overall 34.8% of subjects reported adverse events; there was no significant difference among treatment groups. In addition, drug-related adverse events were reported by 24.7% of study subjects; there was no significant difference among treatment groups. The most common adverse events were in the digestive system (mainly nausea and vomiting), occurring in 30.2% of study subjects. There was no significant difference among treatment groups; it is therefore most likely that these symptoms represent the normal sequelae of a migraine headache attack. No serious adverse events or deaths were reported. Three subjects discontinued therapy due to adverse events, two subjects in the ibuprofen 400 mg group and one subject in the placebo group.

Conclusions: Ibuprofen at OTC doses of 200 mg and 400 mg is an effective treatment for the temporary relief of migraine headache pain and the associated symptoms of migraine including photophobia and functional disability.

Efficacy results for subjects with severe migraine pain intensity are not inconsistent with the current labeling regarding OTC ibuprofen dosing which directs consumers to take 400 mg if pain does not respond to 200 mg.

All secondary efficacy measures including pain relief and pain intensity difference showed effects consistent with the primary efficacy outcome measures.

Ibuprofen was well tolerated and no safety issues were identified in this migraine headache population. There were no significant differences between either dose of ibuprofen and placebo in the incidence of adverse events. The severity and nature of adverse events were similar among groups. No serious adverse events or deaths were reported.

Date of the report: